REMARKS

In the Action, the examiner has maintained the previously issued restriction requirement and rejected pending claims 81-84 under 35 U.S.C. § 112, first paragraph, as assertedly lacking an enabling disclosure.

I. Explanation of claim amendments.

New claims 94-96 are added and are directed to the subject matter elected by the applicant in response to the restriction requirement date August 18, 2006. Support for new claims 94-96 can be found, for example, in original claims 82-84. Accordingly, these amendments do not constitute new matter.

II. The restriction requirement is still improper.

Applicant's response to the restriction requirement set forth numerous defects in the restriction requirement, including, for example, the fact that no reasons were given for the restriction and that the groups were, in fact, overlapping, rather than independent or distinct.

In the outstanding Office action, the Patent Office failed to address any of these reasons, but maintained the restriction requirement and made it final. The basis now offered for the restriction is that separate classification has been established for each group. The applicant does not agree that separate classification in the PTO's classification system, which is merely a convenience tool for searching, is indicative of separate status "in the art." However, a review of the restriction requirement shows that **all thirteen groups were assigned to Class 512, and eleven of thirteen were assigned to subclass 12.** Thus, applying the criteria chosen by the Patent Office, the restriction is improper on its face. With respect to classification, applicant also observes that the parent patent, with claims directed to similar subject matters, was assigned class 424/143.100.

The applicant's attempt to resolve these disagreements concerning the restriction requirement with the examiner and his supervisor were denied in view of the issuance of a first action. Thus, this paper is accompanied by a petition requesting review of the restriction requirement.

III. Priority and Objection to the Specification

The examiner objected to the specification for allegedly failing to properly identify the relationship associated with various priority applications. The present application claims priority to one application (i.e., U.S. Application Serial No. 09/169,079, now U.S. Patent No. 6,824,777). The preliminary amendment dated February 9, 2004 amended the priority claim to include only one

priority application and also properly amended the cross-reference paragraph to indicate that "[t]his application is a continuation of U.S. Application Serial No. 09/169,079." Upon entry of this amendment, the cross-reference paragraph has been amended to update the status of U.S. Application Serial No. 09/169,079.

The examiner further requests that the applicant amend the cross-reference paragraph to reflect the status of further alleged priority applications listed on page 3 of the Office Action. The applications cited by the examiner, however, do not relate to the present application because as they are directed to unrelated subject matter (i.e., CTLA-8 nucleic acids and proteins) and also because said applications were filed by applicants other than the applicant of the present application.

IV. The rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

The examiner rejected claims 81-84 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant requests reconsideration in view of the following remarks.

First, it should be noted that the claims are drawn to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 in blood vessels. The examiner's assertion that the claims are broad "because the recitation of claims 81-84 encompasses the formation of old and new blood vessels from existing vessels by angiogenesis and new blood vessels by vasculogenesis" is misplaced. The pending claims are limited to a method of inhibiting genesis of blood vessels in a mammalian organism in the instance when the mammalian organism has *a disease characterized by Flt4 expression in blood vessels* and not inhibiting genesis of blood vessels in general.

It appears that the examiner's principle concern focuses on the fact that the role of Flt4 (VEGFR-3) in lymphangiogenesis is well established, but its role in genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 in blood vessels is allegedly not predictable.

The examiner cites Tammela et al, (Cardiovasc. Res., 550-563, 2005) and Ferrara et al. (Nature Med., 5:1359-1364, 1999) in support of this rejection. While Tammela et al. report that VEGFR-3 becomes restricted to lymphatic endothelial cells in adults, it further states that VEGFR-3 is also up-regulated on blood vascular endothelial cells in pathologic conditions, such as vascular

tumors and in the periphery of solid tumors. Thus, the teachings of Tammela et al. are consistent with the teachings of the present application and confirm that VEGFR-3 is expressed in the blood vasculature of certain tumors.

The examiner cites Ferrara et al. as evidence that VEGF-C is not involved with the formation of new blood vessels from existing blood vessels. In particular, Ferrera et al. review the findings of Jeltsch et al. (Science, 276:1423-1425, 1997) and Oh et al. (Dev. Biol., 188:96-109, 1997). Jeltsch et al. report that overexpression of VEGF-C in the skin of transgenic mice resulted in lymphatic, but not vascular, endothelial proliferation and vessel enlargement. Oh et al. report that recombinant VEGF-C stimulated lymphatic vessel hyperplasia in mature chick chorioallantoic membrane. The teachings of Jeltsch et al. and Oh et al. cannot be used to demonstrate the unpredictability in the art with respect to the current claims because neither Jeltsch et al. nor Oh et al. utilized a model for a disease characterized by *Flt4 expression in blood vessels* in their experiments. The present claims are directed to methods of anti-Flt4 therapy for inhibiting genesis of blood vessels in a mammalian organism having a disease *characterized by expression of Flt4 expression in blood vessels*, and not to anti-Flt4 therapy that will result in an anti-angiogenic effect in healthy adult tissues. Therefore, it is not surprising that the art does not teach or suggest that VEGF-C and Flt4 play a role in angiogenesis/vasculogenesis in tumors because the first disclosure of such a teaching is in the present application.

As discussed in the specification, Flt4 expression, while largely restricted to the lymphatic endothelia of healthy adults, has been identified in the blood vasculature surrounding at least certain tumors. Example 28 of the present specification teaches that several PAL-E (a blood vessel endothelial marker) positive blood vessels in two types of intraductal carcinomas were also positive for Flt4. The data and subsequent data establish that Flt4 is expressed in the blood vasculature of certain tumors. Results reported in Example 28 indicated that Flt4 expression is up-regulated in breast carcinomas during angiogenesis associated with tumor growth. The highly elevated number of Flt4 positive vessels found in carcinoma *in situ* is compatible with the hypothesis that the carcinoma cells produce factors that bind to and activate receptor tyrosine kinases to stimulate the growth of blood vessels in the immediate vicinity of the carcinoma cells. Example 28 further reports that both intraductal and invasive carcinoma cells often stained positive for VEGF-C protein. Accordingly, one of skill in the art would realize from the specification that the use of an agent that blocks the VEGF-C or VEGF-D stimulation of Flt4 (or VEGFR-2) may be used to inhibit the growth of Flt4 (or VEGFR-2) positive vessels in the carcinomas.

The examiner further asserts that the specification does not provide guidance or direction regarding how Flt4 is involved in the formation of blood vessels and how the inhibition for the genesis of blood vessels can be mediated through Flt4. The examiner states "[s]ince applicants have not linked the expression of Flt4 with the formation of blood vessels, Flt4 may not have any effects on the formation of blood vessels." In response, submitted herewith is a declaration executed by Dr. Kari Alitalo which confirms the role of Flt4 in angiogenesis and tumor growth, and provides evidence that inhibitors of Flt4 are effective to inhibit tumor angiogenesis and tumor growth.

Data published subsequent to the filing of the present application demonstrate that the invention described in the specification as filed can be practiced successfully. Laakkonen et al. (Cancer Res., 67:593-599, 2007) reports that VEGFR-3 is involved in tumor angiogenesis and growth. Laakkonen et al. designed experiments to determine if an inhibitor that prevented ligand binding to VEGFR-3 (Flt-4) could inhibit primary tumor growth and/or tumor angiogenesis *in vivo*. Results indicated that the blood vessel density of tumors treated with an anti-VEGFR-3 antibody was significantly decreased when compared with blood vessel density of tumors treated with the control antibody. Further, when the effect of an VEGFR-3 antibody in the early phases on tumor growth was studied, results indicated that inhibition of tumor growth was already evident after four injections of the VEGFR-3 antibody. The effects of an VEGFR-3 antibody on the later stages of primary tumor growth were also investigated. Results indicated that the VEGFR-3 antibody inhibited the subcutaneous growth of several different tumor cell lines in nude mice. Further, variable inhibition of primary tumor growth by 30% to 44% occurred in xenograft models of various carcinomas when treated with the VEGFR-3 antibody. Thus, Laakkonen et al. provide data which indicate that blocking of the VEGFR-3 pathway inhibits angiogenesis in various tumors. The Laakkonen study and a study by another research group are discussed in the accompanying Rule 132 declaration of inventor Kari Alitalo.

In view of the foregoing, applicant respectfully requests that the rejections of claims 81-84 under 35 U.S.C. § 112, first paragraph (enablement), should be withdrawn.

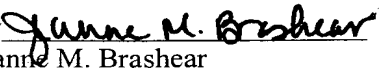
V. Conclusion

For the foregoing reasons, applicant requests withdrawal of all outstanding rejections and allowance of the pending claims. No other fees are believed to be due with the filing of this paper. However, the Director is authorized to charge any additional fees deemed necessary to Deposit Account No. 13-2855, under order number 28967/34891.1.

If the examiner believes that a telephone conversation would expedite allowance of the claims, he is invited to contact the undersigned agent or David A. Gass, attorney for applicant, at the number below.

Dated: March 20, 2007

Respectfully submitted,

By 

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